

IADSA comments on the Draft WHO/FAO Report on Diet, Nutrition and the Prevention of Chronic Diseases

IADSA was founded in March 1998 and now brings together 35 associations of manufacturers and suppliers across the world. IADSA's core role is to help share leading regulatory and scientific information among opinion formers. IADSA is accredited to Codex and is consulted by a range of other international regulatory bodies.

IADSA very much welcomes the opportunity to comment on the reports prepared by the Joint WHO/FAO consultation and, following consultation with the scientific experts working with IADSA member associations and their members, would like to make the following comments.

General Comment

Scientific data and recommendations deal with situations in the developing world where lack of food, poor sanitation, and micronutrient deficiencies are still prevalent. The report correctly acknowledges that the micronutrient deficiencies prevalent in many populations of the developing world contribute significantly to the occurrence of chronic diseases addressed by WHO. Disappointingly, this fact is not reflected in the recommendations of the report. It would seem to be a fundamental claim of the recommendations that each individual should receive their basic requirements of micronutrients (RDA) to prevent the occurrence of nutritional deficiency diseases. We would strongly recommend the inclusion of this point in the recommendations as well as in the implementing strategies.

Criteria used for: “Strength of Evidence”

There appears to be some degree of inconsistency in the method of categorising the strength of evidence that provides the basis for the summary in Annex 1. Clinical evidence of equivalent validity appears to be treated differently according to the dietary /nutrition practice-disease relationship, and the importance given to epidemiological evidence seems to vary.

To illustrate this point, one can examine the proposed categorisation of trans-fatty acids, in comparison to that of plant sterols/stanols or Vitamin E supplements in the context of cardiovascular disease (CVD). It is considered that there is “convincing” evidence demonstrating a relationship between trans-fatty acids and the increased risk of CVD. However, the evidence that plant sterol/stanols decrease the risk of CVD is estimated to be “probable”. In reality, the data from the trans-fatty acid randomized control trials (RCT) tends to be inconsistent in comparison with the data on plant sterol/stanol. What differentiates the trans-fatty acid data from the plant sterols/stanols data is the consistency of the epidemiological data which, one assumes, must therefore be the basis for the categorisation as “convincing”. Neither trans-fatty acids nor plant sterol/stanols have been examined directly in a RCT in relation to the endpoint of CVD (mortality/recurring MI) either in a primary or secondary prevention scenario.

For vitamin E on the other hand, as for trans-fatty acids, epidemiological studies have consistently shown a potential beneficial effect in decreasing CVD risk besides other antioxidant vitamins (vitamins C and beta-carotene). Animal model studies and mechanistic studies provide strong plausibility for the epidemiological results.

Intervention studies with vitamin E (and other antioxidants) have revealed inconsistent outcomes. Attachment 1 provides a summary of recent intervention studies and their outcomes as well as a list of ongoing intervention studies. Results from intervention studies such as LINXIAN, CHAOS and GISSI indicate a reduced risk of CVD: reduction in CVD death (CHAOS and GISSI), non-fatal myocardial infarction (CHAOS) and decrease in cerebrovascular risk (LINXIAN). Several aspects may significantly contribute to the inconsistent outcomes of the intervention trials: Firstly, the limited duration of the intervention in these populations may not replicate lifetime exposure. Secondly, the trials have been performed in people with a high risk of cardiovascular events, often being

treated with drugs for an existing condition. Epidemiological studies compare the lowest quintile with the highest one, whereby the lowest quintile is very often close to deficiency. However, intervention trials are done in a randomized population that is equivalent to comparing the fourth quintile with the fifth quintile. Thus, the placebo group may already fulfil the proposed requirement for the tested nutrients.

The treatments leading to normalization of cholesterol or blood pressure and/or diabetes are known to reduce the risk of coronary heart disease by themselves. Thus, supplementation with antioxidant vitamins for short periods to those at a high-risk and under drug treatment for pre-existing conditions, may not reveal the additional reduction of cardiovascular risk. The question, therefore, still remains unanswered as to whether vitamin E and other antioxidant vitamins may be beneficial in preventing atherogenesis at an earlier stage of the disease or in a population with a marginal supply of antioxidants (Kaul et al 2001; Pryor 2000; Witztum and Steinberg 2001). Intervention trials in normal populations with no previous clinical history of cardiovascular events would help to evaluate the potential of antioxidant vitamins in decreasing the occurrence of cardiovascular events as has been predicted in animal studies and supported by epidemiological studies. Several intervention studies, especially with combinations of antioxidant vitamins and other nutrients are ongoing and the results will be available in the coming years (PHS II, SU.VI.MAX , WHS).

Whereas in the case of vitamin E, epidemiological evidence is disregarded, this sort of evidence seems to be pivotal in the categorisation of trans-fatty acids. Likewise, little consideration is given to the lack of outcomes in hard endpoints regarding CVD for trans-fatty acids but this is into central to the categorisation of plant sterols/stanols. We would therefore suggest that the scientific panel reconsider their categorisation to ensure that a consistent approach is used across the whole report.

In the case of vitamin E, we believe that the inconsistencies experienced in clinical trials and their contradiction with the results of epidemiological studies make it difficult to conclude "convincingly" that there is no relationship between vitamin E and CVD. On the contrary, the totality of the evidence would suggest a *probable* decrease in risk of CVD associated with supplementation of dietary antioxidants.

ACRONYMS

HPS	Heart Protection Study
HOPE	Heart Outcome Prevention Evaluation
SECURE	Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E
LINXIAN	Linxian General Population Intervention Trials
CHAOS	Cambridge Heart Antioxidant Study
GISSI	Gruppo Italiano per lo Studio Della Sopravvivenza nell'Infarto Miocardico
PHS II	Physicians' Health Study II
SU.VI.MAX	Supplementation Vitamins Minerals Anti-oXidants
WHS	Women's Health Study

References:

Kaul, Devaraj, Jialal. Alpha-Tocopherol and Atherosclerosis. Proc Soc Exp Biol Med 2001;226:5-12.

Pryor WA. Vitamin E and Heart Disease: Basic Science to Clinical Intervention Trials. Free Radical Biol Med 2000;28:141-164.

Witztum JL, Steinberg D. The Oxidative Modification Hypothesis of Atherosclerosis: Does It Hold for Humans? Trends Cardiovasc Med 2001;11:93-102.

Beta-carotene and Cardiovascular diseases

The table represented in Annex 1 concludes that scientific evidence available demonstrates that beta-carotene supplements increase the risk of cardiovascular death. The authors rated the evidence as *probable*.

The authors base their decision and rating on a meta-analysis published by Egger et al in 1998 in BMJ and cited by Ness. The meta-analysis combines four intervention

studies; the ATBC, CARET, Physicians' Health Study (PHS) and the Greenberg Skin Cancer Study. With the exception of the PHS, these studies were conducted as cancer prevention trials, mostly in active or former smokers (63 - 100 %). None of the studies found a significant increase of the cardiovascular risk in the β -carotene supplemented groups.

The original publication from the PHS, the only study that is relevant for the general population, clearly indicates that the relative risk of mortality from cardiovascular disease associated with supplemental beta-carotene in non-smokers is 1.00.

The outcome of the meta-analysis is misleading since it is based on a pooled sample mainly of smokers. Since only 17% of the subjects were non-smokers the results are confounded by a disproportionate representation of smokers at risk of cardiovascular mortality.

The results of the PHS have recently been confirmed by the Heart Protection Study, Oxford, with 20536 participants. The supplementation of β -carotene, together with vitamin E and vitamin C, did not produce any adverse effects on vascular or non-vascular morbidity or mortality (Collins et al). Sir Richard Peto, Oxford, the founder of Meta-analysis who was involved in several of the big intervention trials, does not share the view of beta-carotene having adverse effects (personal communication).

There is therefore insufficient evidence to draw conclusions about the relationship between beta-carotene supplements and cardiovascular disease.

References

Egger M, Schneider M, and Smith G. *Meta-analysis* Spurious precision? Meta-analysis of observational studies. *BMJ* 1998; 316:140-144.

Ness AR. Commentary: beyond beta-carotene - antioxidants and cardiovascular disease. *Int J Epidemiol* 2001; 30: 143-144

Collins et al: The Heart Protection Study. *Circulation* 2002; 105:e37-e41

Vitamin E and Periodontal Disease

Vitamin E is mentioned in the context of several disease conditions as having no effect or low/insufficient evidence to be related to certain disease conditions; one of these is periodontal disease. We are sure there are also many other nutrients and bioactive components that are also known not to have an effect under the disease condition under consideration. However, these substances are not mentioned. This repetitive situation for Vitamin E may have an unfair “negative image” effect on this vitamin. We suggest deleting “Vitamin E supplementation” from the no-relationship column on table 11 (page 40).

Vitamin K and Osteoporosis

The report mentions in Annex 7 on page 17 that various nutrients such as vitamins C, A, K, and sodium may also play an important role for long-term bone health and the prevention of osteoporosis, however, according to the authors, the evidence from physiological and clinical studies were largely lacking. One of the nutrients listed is vitamin K.

Considering the entire database available for vitamin K - including several clinical trials and the biological plausibility, the role of vitamin K in osteoporosis is clearly underestimated in the report (Weber 2001, Vermeer et al 2001). In fact, it does not correctly represent the current state of scientific knowledge. Considering the latest literature, the available data would justify a dedicated paragraph on the role of vitamin K in osteoporosis similar to the paragraph on magnesium where the available scientific data is even less. In a study with 190 subjects, it has been demonstrated that vitamin K2 not only increases γ -carboxylation of osteocalcin, but also it prevents fractures (Shiraki 2000).

Therefore we would suggest the inclusion of a paragraph including the following elements related to vitamin K:

- *In the last decade it has become evident that vitamin K has a significant role to play in human health which is beyond its well-established function in blood clotting.*
- *There is a consistent line of evidence in human epidemiological as well as in human intervention studies, which clearly demonstrates that vitamin K can improve bone health. The human intervention studies have not only demonstrated that vitamin K can increase bone mineral density in osteoporotic people but have also shown that vitamin K can actually reduce fracture rates.*
- *Furthermore, there is evidence in human intervention studies that vitamins K and D, a classic in bone metabolism, may work synergistically on bone density. Most of these studies employed vitamin K₂ at rather high doses, a fact that has been criticized as a shortcoming of these studies.*
- *However, there is emerging evidence in human intervention studies that vitamin K₁ at a much lower dose may also benefit bone health in particular when co-administered with vitamin D.*
- *Several mechanisms are suggested by which vitamin K can modulate bone metabolism. Besides the γ -carboxylation of osteocalcin, a protein believed to be involved in bone mineralization, there is increasing evidence that vitamin K₁ may also positively affect Ca balance, a key mineral in bone metabolism.*

References

Weber P. Vitamin K and Bone Health. Nutrition 2001;17:880-887.

Vermeer C, Braam L. Role of K Vitamins in the Regulation of Tissue Calcification. J Bone Metab 2001;19:201-206.

Shiraki M, Shiraki Y, Aoki C, and Miura M. J Bone Miner Res 2000; 15: 515-521

Table I: Major Completed Intervention Studies with Antioxidant Vitamins and CVD

Study	Participants	Parameters	Intervention	Outcome
ATBC	29133 male smokers primary prevention in risk groups	long-term effect on cancer incidence and mortality CVD incidence	50 IU vitamin E 20 mg beta-carotene combination placebo on average 6 years	no effect on mortality no significant effect on CVD vitamin E: increase in hemorrhagic stroke, decrease in ischemic stroke
LINXIAN	29584 men and women primary prevention	long-term effect on cancer mortality CVD incidence and mortality	Combination: 50 IU vitamin E 20 mg beta-carotene 50 microg selenium more than 5 years	trend in decrease of cerebro- vascular risk
CARET	18314 smokers and asbestos exposed men and women primary prevention in a risk group	Lung cancer; cancer mortality CVD incidence	combination: 25000 IU vitamin A 30 mg beta-carotene on average of 4 years	no significant effect on CVD
PHS I	22000 male physicians primary prevention	mortality / incidence of CVD	50 mg beta-carotene on alternate days 12 years	no benefit / no harm subgroup analyses in high risk group with previous angina possible reduction in CVD events
HPS	20000 men/ women with CVD risk factors or events secondary prevention	CVD mortality, stroke, MI all cancer mortality	combination of 600 mg Vit E, 250 mg Vit C, 20 mg Beta-carotene 40 mg simvastatin; placebo	no benefit / no harm

Study	Participants	Outcome Parameters	Intervention	Outcome
ASAP	520 men / women with elevated cholesterol	atherosclerosis progression	136 IU vitamin E 250 mg vitamin C combination 3 years	combination retards progression in carotid atherosclerosis
PPP	4495 men / women with one or more CVD risk factors	death from CVD total CVD events	100 mg aspirin 300 IU vitamin E 3.6 years	vitamin E did not show any effect possibly due to inadequate power of prematurely interrupted trial
CHAOS	2002 patients with proven coronary atherosclerosis secondary prevention	CVD death non-fatal MI	400-800 IU vitamin E 510 days	reduction in CVD death reduction in risk for non-fatal MI
GISSI	11324 patients with MI secondary prevention	CVD death non-fatal MI stroke	300 IU vitamin E 3.5 years	no effects on primary endpoints significant 20% reduction in CVD death in vitamin E group vs control
HOPE	9541 men/women with existing CVD secondary prevention	CVD death, MI stroke incidence	ACE inhibitor 400 IU vitamin E mean of 4.5 years	no differences vs placebo
SECURE	732 subjects from HOPE secondary prevention	progression of carotid atherosclerosis intima changes	400 IU vitamin E 4.5 years	neutral effect of vitamin E
SPACE	196 patients with endstage renal disease secondary prevention	fatal /non-fatal MI stroke unstable angina	800 IU vitamin E mean of 519 days	significant 46% reduction in incidence of primary endpoints significant reduction in MI number no effect on total and CVD death